1.6.1 Prescribing information (Summary of Product Characteristics / SmPC)

1. Name of Medicinal Product

1.1 Product Name: Vintor 4000

1.2 Strength:

Each vial/prefilled syringe contains

Erythropoietin Concentrated solution Ph. Eur. 4000 IU

1.3 Dosage Form: Injectable

A clear, colourless solution virtually free from particles

2. Quality and Quantitative Composition

Vintor 4000

Each vial/prefilled syringe contains:

Erythropoietin Concentrated solution Ph. Eur. 4000 IU

Single-dose, Preservative-free Pre-Filled Syringe (PFS): Each 1 mL of solution contains 4000 IU of Erythropoietin (as Erythropoietin Concentrated Solution Ph. Eur.), 2.5 mg Albumin (Human), 5.8 mg Sodium Citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in Water for Injections, Ph. Eur. (pH 6.9 ± 0.3). This formulation contains no preservative.

3. Pharmaceutical Form

Sterile clear solution for intravenous or subcutaneous injection

A clear, colourless solution virtually free from particles

Vintor is presented as a sterile, colorless liquid in an isotonic sodium chloride/sodium citrate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of anaemia of chronic renal failure patients:

r-Hu-EPO is indicated for the treatment of anaemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. Non-dialysis

patients with symptomatic anaemia considered for therapy should have a hemoglobin less than 10 g/dl. r-Hu-EPO is not intended for patients who require immediate correction of severe anaemia. r-Hu-EPO may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion. Prior to initiation of therapy, the patient's iron stores should be evaluated.

Treatment of anaemia in zidovudine-treated HIV-infected patients: r-Hu-EPO is indicated for the treatment of anaemia related to therapy with zidovudine in HIV-infected patients. r-Hu-EPO is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. r-Hu-EPO is effective in HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤ 500 mUnits/ml and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

Anaemia of prematurity:

For the treatment of iron deficiency anaemia during pregnancy: r-Hu-EPO therapy is effective in stimulating erythropoiesis in very low birth weight infants. Although the optimal timing of r-Hu-EPO therapy in premature infants remains unresolved, it is suggested that treatment with r-Hu-EPO should be initiated before anaemia becomes symptomatic in such patients.

Treatment of anaemia in cancer patients on chemotherapy: Erythropoietin is indicated for the treatment of anaemia in patients with non-myeloid malignancies where anaemia is due to the effect of concomitantly administered chemotherapy. r-Hu-EPO is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months.

Reduction of allogeneic blood transfusion in surgery patients: r-Hu-EPO is indicated for the treatment of anemic patients (hemoglobin >10 to ≤ 13 g/dl) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need fo allogeneic blood transfusions. The safety of the pre-operative use of r-Hu-EPO has been studied only in patients who are receiving anticoagulant prophylaxis.

4.2 Posology and method of administration

- Do not shake and/or freeze.
- Do not use any formulation exhibiting particulate matter or discoloration.
- Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, erythropoietin from vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort.

4.3 Contraindications

- Uncontrolled hypertension.
- Known hypersensitivity to mammalian cell-derived products.
- Known hypersensitivity to Albumin (Human).

4.4 Special warning and precautions for use

Precautions

The parenteral administration should be attended by appropriate precautions in case allergic or other untoward reactions occur.

Hematology: Exacerbation of porphyria has been observed rarely in patients with CRF treated with r-Hu-EPO. Thus it should be used with caution in patients with known porphyria.

Lack or loss of response: If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

1. Iron deficiency
2. Underlying infectious, inflammatory, or malignant processes.
3. Occult blood loss.
4. Underlying hematologic diseases (i.e., thalassemia, refractory anemia, or other myelodysplastic disorders).

5. Vitamin deficiencies: Folic acid or vitamin B12.

6. Hemolysis.

7. Aluminum intoxication.

8. Osteitis fibrosa cystica.

9. Pure Red Cell Aplasia (PRCA): In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to recombinant erythropoietins.

Iron evaluation: During r-Hu-EPO therapy, absolute or functional iron deficiency may develop. Prior to and during erythropoietin therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 % and ferritin should be at least 100 ng/ml. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by erythropoietin.

4.5 Interaction with other medicinal products and other forms of interactions

There is no evidence of interaction r-Hu-EPO with other drugs.

4.6 Pregnancy and lactation

Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. r-Hu-EPO should be used during pregnancy only if potential benefit justifies the potential risk to the fetus. It is not known whether is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when erythropoietin is administered to a nursing woman.

Nursing mothers: It is not known whether is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when erythropoietin is administered to a nursing woman.

4.7 Effects on ability to drive and use machine

Not relevant.

4.8 Undesirable effects

r-Hu-EPO is generally well-tolerated. The most prevalent adverse effect associated with r-Hu-EPO is hypertension. Other adverse effects include headache, arthralgia, nausea, edema, fatigue, diarrhoea, vomiting, chest pain, injection site skin reaction, asthenia, dizziness, hyperkalemia, venous fistula clotting, functional iron deficiency, and rare reports of thrombocytosis, sweating, and bone pain. Rarely thrombo-embolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins have been reported with r-Hu-EPO. As with all therapeutic proteins, there is the potential for immunogenicity.

4.9 Overdose

The maximum amount of r-Hu-EPO that can be safely administered in single doses has not been determined. Doses of up to 1500 IU/kg TIW for 3 to 4 weeks have been administered to adults without any direct toxic effects of r-Hu-EPO itself. Therapy with can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, r-Hu-EPO may be temporarily withheld until the hemoglobin returns to the suggested target range; r-Hu-EPO therapy may then be resumed using a lower dose. If polycythemia is of concern, phlebotomy may be indicated to decrease the hemoglobin.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

ATC Classification: B03XA01

Erythropoietin is a glycoprotein that stimulates, as a mitosis-stimulating factor and differentiating hormone, the formation of erythrocytes from precursors of the stem cell compartment.

The apparent molecular weight of erythropoietin is 32,000 to 40,000 dalton. The protein fraction of the molecule contributes about 58% and consists of 165 amino acids. The four carbohydrate chains are attached via three N-glycosidic bonds and one O-glycosidic bond to the protein. Epoetin alfa obtained by gene technology is glycosylated and is identical in its amino acid and carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients.

Epoetin alfa has the highest possible purity according to the present state of the art. In particular, no residues of the cell line used for the production are detectable at the concentrations of the active ingredient that are used in humans.

The biological efficacy of epoetin alfa has been demonstrated in various animal models in vivo (normal and anaemic rats, polycythaemic mice). After administration of epoetin alfa, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

An increased 3H-thymidine incorporation in the erythroid nucleated spleen cells has been found in vitro (mouse spleen cell culture) after incubation with epoetin alfa.

It could be shown with the aid of cell cultures of human bone marrow cells that epoetin alfa stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of epoetin alfa on bone marrow cells could not be detected.

721 cancer patients receiving non-platinum chemotherapy were included in three placebo-controlled studies, 389 patients with haematological malignancies (221 multiple myeloma, 144 non-Hodgkin's lymphoma and 24 other haematological malignancies) and 332 with solid tumours (172 breast, 64 gynaecological, 23 lung, 22 prostate, 21 gastrointestinal, and 30 other tumour types). In two large, open-label studies, 2697 cancer patients receiving non-platinum chemotherapy were included, 1895 with solid tumours (683 breast, 260 lung, 174 gynaecological, 300 gastrointestinal, and 478 other tumour types) and 802 with haematological malignancies.

In a prospective, randomised, double-blind, placebo-controlled trial conducted in 375 anaemic patients with various non-myeloid malignancies receiving non-platinum chemotherapy, there was a significant reduction of anaemia-related sequelae (e.g. fatigue, decreased energy, and activity reduction), as measured by the following instruments and scales: Functional Assessment of Cancer Therapy-Anaemia (FACT-An) general scale, FACT-An fatigue scale, and Cancer Linear Analogue Scale (CLAS). Two other smaller, randomised, placebo-controlled trials failed to show a significant improvement in quality of life parameters on the EORTC-QLQ-C30 scale or CLAS, respectively.

Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

Survival and tumour progression have been examined in five large controlled studies involving a total of 2833 patients, of which four were double-blind placebo-controlled studies and one was an open-label study. The studies either recruited patients who were being treated with chemotherapy (two studies) or used patient populations in which ESAs are not indicated: anaemia in patients with cancer not receiving chemotherapy, and head and neck cancer patients receiving radiotherapy. The target haemoglobin concentration in two studies was>13 g/dl; in the remaining three studies it was 12-14 g/dl. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.

A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radio-, chemoradio-, or no therapy) participating in 53 controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favour of controls (95% CI: 1.00, 1.12; 53 trials and 13,933 patients) and for the cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10,441 patients). Meta-analyses also indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin.

5.2 Pharmacokinetic Properties

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin after intravenous administration ranges from 4 to 13 hours. The half-life is approximately 20 % longer in CRF patients than that in healthy subjects. After subcutaneous administration, peak plasma levels are achieved within 5 to 24 hours. The half-life is similar between adult patients with serum creatinine level greater than 3 mg/dl and not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in r-Hu-EPO half-life among adult patients above or below 65 years of age. The pharmacokinetic profile of r-Hu-EPO in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.

5.3 Preclinical safety Data

Acute Toxicity Studies:

1. ***Acute Intravenous toxicity study in Sprague Dawley Rats:***

The study was designed to determine the acute intravenous toxicity of Erythropoietin to Sprague Dawley rats. No signs of intoxication were observed in animals treated at the dose levels of 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities

attributable to the treatment. It was concluded that the acute lethal intravenous dose of Erythropoietin in Sprague Dawley rats was found to be greater than 10000 IU/kg body weight.

2. ***Acute Intravenous toxicity study in Swiss Albino Mice:***

   The study was designed to determine the acute intravenous toxicity of Erythropoietin to Swiss Albino mice. No signs of intoxication were observed in animals treated at the dose levels of 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute lethal intravenous dose of Erythropoietin in Swiss Albino mice was found to be greater than 10000 IU/kg body weight.

3. ***Acute Intravenous toxicity study in New Zealand White Rabbits:***

   The study was designed to determine the acute intravenous toxicity of Erythropoietin to New Zealand White rabbits. No signs of intoxication were observed in animals treated at the dose levels of 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute lethal intravenous dose of Erythropoietin in New Zealand White rabbits was found to be greater than 10000 IU/kg body weight.

4. ***Acute subcutaneous toxicity study in New Zealand White rabbits:***

   The study was designed to determine the acute subcutaneous toxicity of Erythropoietin to New Zealand White rabbits. No signs of intoxication were observed in animals treated at the dose levels of 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute

lethal subcutaneous dose of Erythropoietin in New Zealand White rabbits was found to be greater than 10000 IU/kg body weight.

5. ***Acute subcutaneous toxicity study in Sprague Dawley Rats:***

   The study was designed to determine the acute subcutaneous toxicity of Erythropoietin to Sprague Dawley rats. No signs of intoxication were observed in animals treated at the dose levels of 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute lethal subcutaneous dose of Erythropoietin in Sprague Dawley rats was found to be greater than 10000 IU/kg body weight.

6. ***Acute subcutaneous toxicity study in Swiss Albino Mice:***

   The study was designed to determine the acute subcutaneous toxicity of Erythropoietin to Swiss Albino mouse. No signs of intoxication were observed in animals treated at the dose levels of 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute lethal subcutaneous dose of Erythropoietin in Swiss Albino mice was found to be greater than 10000 IU/kg body weight.

Sub-Chronic Toxicity Studies:

7. ***Subchronic subcutaneous Toxicity study in Swiss Albino Mice***

   The sub-chronic subcutaneous toxicity study was designed and conducted to determine the toxicity profile of Erythropoietin when administered daily for 28 days in Swiss Albino mice. Erythropoietin was administered to animals at the dose levels 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight. Two additional dose levels were added to the study as 0 IU/kg and 10000 IU/kg, in order to study the reversibility or delayed occurrence of symptoms, if any. The control animals were administered with vehicle only.

All the male and female animals from control and different dose groups up to 10000 IU/kg survived through the dosing period 28 days and the recovery period of 14 days No signs of intoxication were observed in animals from different dose groups during the dosing period of 28 days and during the recovery period of 14 days. Male and animals from different dose groups exhibited comparable body weight gain with that of respective controls throughout the dosing period of 28 day and the recovery period of 14 days. Food consumption of control and treated animals was found to be comparable throughout the dosing period of 14 days. Haematological analysis conducted at the end of the dosing period on day 29 revealed decreased reticulocyte values in male and female animals from 10000IU/kg dose group and haematological analysis conducted at the end of post-dosing recovery period on day 43, revealed no abnormalities attributable to the treatment. Biochemical analysis did not reveal any abnormalities attributable to the treatment. Urine analysis of all the animals, conducted in week 4 and reversal group animals in week 6, revealed no abnormality. Organ weight data of male and females sacrificed on day 29, from controls and all treated dose groups was found to be comparable. Organ weight data of male and female animals from 10000 IU/kg reversal group sacrificed on day 43, was found to be comparable with that of respective controls. Gross pathological and histopathological examination did not reveal any abnormality.

8. ***Subchronic subcutaneous Toxicity study in New Zealand White Rabbit:***

The sub-chronic subcutaneous toxicity study was designed and conducted to determine the toxicity profile of Erythropoietin when administered daily for 28 days to New Zealand white Rabbit. Erythropoietin was administered to rabbits via subcutaneous route at the dose levels ranging from 0 IU/kg, 2500 IU/kg, 5000 IU/kg and 10000 IU/kg body weight.

All the male and female animals from control and different dose groups survived through the dosing period 28 days. No signs of intoxication were observed in animals from different dose groups during the dosing period of 28 days. Male and animals from control and different dose groups exhibited normal body weight gain at the end dosing period of 28 day. Food consumption of control and

treated animals was found to be comparable throughout the dosing period of 28 days. Haematological analysis revealed no abnormalities attributable to the treatment. Biochemical analysis, Gross pathological examination, Histopathological examination did not reveal any abnormalities attributable to the treatment. Organ weight data of male and female animals from control and different dose groups was found to be comparable over a period of 7 days was found to be 2.5 mg/kg in male and female animals.

6. Pharmaceutical Particulars

6.1 List of excipients

PFS or Single dose vial

Human Serum Albumin

Sodium Chloride

Tri Sodium Citrate

Citric Acid Monohydrate

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

6.3 Shelf life

24 months from the date of manufacturing, when stored as described below.

6.4 Special precautions for storage

Store between 2°C to 8°C. Protect from light. Do not freeze or shake.

6.5 Nature and contents of container

Solution for injection in a pre-filled syringe (Type I glass), with a rubber stopper, and with a stainless steel needle OR in a vial (Type I glass) with a rubber stopper.

7. **Marketing Authorization Holder**

   Gennova Biopharmaceuticals Ltd.

   Block 1, Plot No: P-1 & P-2, I.T.B.T. Park, Phase-II,

   M.I.D.C, Hinjawadi, Pune-411 057, **INDIA**

8. **Marketing Authorization Numbers**

   PD/VACC-6 in form 28-D

9. **Date of first authorization/renewal of the authorization**

   14 November 2006/14 November 2011

10. **Date of revision of the text**

    Not Applicable